Noise buffering of gene expression by decoys

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Many eukaryotic transcription factors bind to DNA with a remarkable lack of specificity, resulting in large numbers of high affinity, nonfunctional, "decoy" binding sites. If binding to DNA protects transcription factors from degradation, the steady state mean unbound copy number will be unaffected by the number of decoys. We characterize the ability a collection of identical decoy sites to buffer noise in the unbound transcription factor copy number of an auto-regulated gene. We show this noise buffering is limited to Poisson noise and that the optimum noise buffering decoys have a probability ½ of being bound at mean expression. We also discuss the implications of adding decoy binding sites on increasing the time scales of approach to steady state and epigenetic escape.

***Keywords*— transcriptional regulation, noise buffering**

I. Introduction

New bioinformatical techniques are able to identify where transcription factors prefer to bind in a genome. For some transcription factors, the shear number of these high affinity sites suggests that these sites might serve some unknown function in gene regulation [1]. One would expect that a large number of decoy binding sites would make gene regulation more difficult because they make finding the target regulatory site more difficult to locate. We have shown, however, that if binding to DNA protects transcription factors from degradation, such as with the protein MyoD [2], the effect of competition for binding is canceled out by stabilization from binding, such that the mean unbound copy number of transcription factors does not depend on the number of decoy binding sites [3]. Here we discuss the ability of decoy binding sites to weakly and indirectly effect transcriptional regulation by coupling the unbound transcription factor copy number to a large reservoir of bound transcription factors through binding and unbinding.

II. Methods

We consider a master equation that keeps track of binding site occupancy and transcription factor copy number. We use adiabatic elimination to reduce the dimensionality of the system and make use of the Fokker Planck approximation to derive analytical formulas that agree well with numerical calculations.

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III. Results

A. Decoys reduce gene expression noise and stabilize the states of a multi-stable expression profile.

Although the mean unbound transcription factor copy number is unaffected by adding decoy binding sites, the variance in the unbound copy number is reduced because of a coupling to the reservoir of bound transcription factors. In the limit of adding many decoys, fluctuations in the total copy number from production and degradation events are buffered away once they are projected in the unbound copy number. This effect becomes more pronounced when considering noise from transcriptional and translational bursting.

B. Decoys buffer noise to the limit of Poisson statistics because of the noise resulting from binding and unbinding.

In the limit that the number of decoy binding sites added is very large, the variance of the unbound copy number of transcription factors approaches the mean. In this limit, binding and unbinding rates in the vicinity of a fixed point are effectively constant, resulting in Poisson noise.

C. The optimum noise buffering and peak stabilizing decoys have a ½ probability of being bound at mean expression.

When varying the binding equilibrium constant of the decoys, we show that although all decoys buffer noise, the most efficient noise reducing decoys have a ½ probability of being bound at a fixed point. In the case of bimodal gene expression, the equilibrium constant of the decoys determines which peak is preferentially stabilized over the other.

D. Decoys slow gene expression dynamics.

We show that decoys linearly increase the time for the system to reach steady state and exponentially increase the time to escape from one gene expression state to another. For a given decoy equilibrium constant this effect and the ones described above scale with the ratio of the number of binding sites to the mean unbound transcription factor copy number.

References

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